AU

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 January 2002 (17.01.2002)

PCT

(10) International Publication Number
WO 02/04012 A1

(51) International Patent Classification[7]: A61K 38/14, 47/10, 47/34

(21) International Application Number: PCT/IB01/01176

(22) International Filing Date: 3 July 2001 (03.07.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1360/00 11 July 2000 (11.07.2000) CH

(71) Applicant *(for all designated States except US)*: **MICIO PHARMA CHEMICAL AG** [IT/IT]; c/o Firmata Treuhand Anstalt, Landstrasse 35, Postfach 1138, I-20080 Basiglio (IT).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **DE TOMMASO, Vincenzo** [IT/IT]; Residenza Alberata, 352, I-20080 Basiglio (IT).

(74) Agents: **KLAUSNER, Erich** et al.; Ufficio Internazionale Brevetti Ing. C. Gregorj S.p.A., Via Dogana, 1, I-20123 Milan (IT).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/04012 A1

(54) Title: ANHYDROUS PHARMACEUTICAL COMPOSITION OF VANCOMYCIN FOR TOPICAL USE

(57) Abstract: The present invention refers to an anhydrous pharmaceutical composition of vancomycin, in the form of the free base or a pharmaceutically acceptable salt thereof, for topical use.

ANHYDROUS PHARMACEUTICAL COMPOSITION OF VANCOMYCIN FOR TOPICAL USE

The present invention refers to anhydrous pharmaceutical compositions of vancomycin for topical use.

Vancomycin is a glycopeptide antibiotic having a broad spectrum of antimicrobal activity, principally active against gram-positive bacteria. It inhibits the synthesis of the cell wall in sensitive bacteria by forming complexes with the mucopeptide precursors of this cell structure.

Vancomycin hydrochloride is a white powder, water soluble at concentration higher than 100 mg/ml and it is generally administered intravenously, more rarely orally.

The pharmaceutical compositions of the present invention for topical use are useful for the treatment of dermal infections and furthermore they have the advantage of being very stable.

The anhydrous pharmaceutical compositions for topical use of the present invention comprise:

a) vancomycin,
b) one or more glycols and/or the ethers thereof,
c) one or more fatty acid triglycerides and /or the polyoxyethylene derivatives thereof,
d) a gelling agent.

Vancomycin is present either in the form of the free base or of a pharmaceutically acceptable salt thereof, in particular as hydrochloride.

The glycols and/or the ethers thereof may preferably be ethylene glycol, propylene glycol, diethylene glycol monomethyl ether, diethylene glycol monoethyl ether.

The fatty acid triglicerides and /or the polyoxyethylene derivative thereof are preferably chosen in the group consisting of $C_8, C_{10}, C_{12}, C_{14}, C_{16}, C_{18}, C_{20}$ fatty acid triglicerides and the polyoxyethylene derivatives thereof wherein the

polyoxyethylene has preferably a molecular weight from 200 to 10,000. Labrasol (polyethylene glycol C_{8-10} glycerides) is particularly preferred.

The gelling agent preferably is a cellulose ester or ether, a polymer or copolymer of the acrylic or methacrylic acid, a polymer or copolymer of an acrylic or methacrylic acid ester, xanthan gum, carrageenin.

Vancomycin or a salt thereof is present in an amount varying from 0.01 to 25% by weight of the total composition.

The other ingredients are present in an amount varying from 0.01 to 99% by weight of the total composition.

The component b) preferably is present in an amount varying from 0.1 to 99% by weight of the total composition.

The component c) preferably is present in an amount varying from 0.01 to 30 % by weight of the total composition.

The component d) preferably is present in an amount varying from 0.01 to 15% by weight of the total composition.

Furthermore, the pharmaceutical compositions of the present invention may contain a surfactant which may be non-ionic, anionic or cationic.

Preferred cationic surfactants are the quaternary ammonium salts.

A preferred anionic surfactant is sodium lauryl sulfate.

A preferred non-ionic surfactant is polyoxyethylene stearyl ether.

Furthermore, the pharmaceutical compositions of the present invention may contain an emulsifying agent.

The pharmaceutical compositions of the present invention may be prepared by the usual methods known to a person skilled in the art.

EXAMPLE

Cream for topical use

VANCOMYCIN (free base)	1.0 g
TRANSCUTOL	30.0 g
(diethylene glycol monomethyl ether)	
PROPYLENE GLYCOL	60.0 g
LABRASOL	5.5 g
(polyethylene glycol C_{8-10} glicerides)	
CARBOPOL	3.5 g
(acrylic acid copolymer)	

The above reported amounts of Transcutol, Labrasol and propylene glycol were placed in a suitable tank. The above reported amount of carbopol was added to the mixture, which was then solubilized and homogenized in a turbomixer. The thus formed gel was cooled to 30°C and vancomycin was added thereto. Vancomycin was solubilized with the aid of a turbomixer while maintaining the temperature at 35-40°C.
Plastic tubes were filled with the so obtained homogeneous gel up to a weight of 10 to 20g.

CLAIMS

1) An anhydrous pharmaceutical composition of vancomycin, in the form of the free base or a pharmaceutically acceptable salt thereof, for topical use.
2) An anhydrous pharmaceutical composition according to claim 1 comprising:
   a) vancomycin, in the form of the free base or a pharmaceutically acceptable salt thereof,
   b) one or more glycols and/or the ethers thereof,
   c) one or more fatty acid triglicerides and /or the polyoxyethylene derivatives thereof, and
   d) a gelling agent.
3) An anhydrous pharmaceutical composition according to claim 1 or 2, wherein vancomycin is in the form of hydrochloride.
4) An anhydrous pharmaceutical composition according to claim 1 to 3, wherein vancomycin is present in an amount varying from 0.01 to 25 % by weight of the total composition.
5) An anhydrous pharmaceutical composition according to claims 2 to 4, wherein the component b) is present in an amount varying from 0.1 to 99 % by weight of the total composition.
6) An anhydrous pharmaceutical composition according to claims 2 to 5, wherein the component c) is present in an amount varying from 0.01 to 30 % by weight of the total composition.
7) An anhydrous pharmaceutical composition according to claims 2 to 6, wherein the component d) is present in an amount varying from 0.01 to 15 % by weight of the total composition.

8) An anhydrous pharmaceutical composition according to claims 2 to 7, wherein the glycols and/or the ethers thereof are chosen in the group consisting of ethylene glycol, propylene glycol, diethylene glycol monomethyl ether, diethylene glycol monoethyl ether.

9) An anhydrous pharmaceutical composition according to claims 2 to 8, wherein the fatty acid triglicerides and /or their polyoxyethylene derivatives, are chosen in the group consisting of C_{8-20} fatty acid triglicerides and the polyoxyethylene derivatives thereof wherein the polyoxyethylene has preferably a molecular weight from 200 to 10,000.

10) An anhydrous pharmaceutical composition according to claims 2 to 9, wherein the gelling agent is chosen in the group consisting of cellulose esters or ethers, polymers or copolymers of the acrylic or methacrylic acid, polymers or copolymers of acrylic or methacrylic acid esters, xathan gum, carrageenin.

11) An anhydrous pharmaceutical composition according to claims 2 to 10, furthermore comprising a surfactant.

12) An anhydrous pharmaceutical composition according to claims claims 2 to 11, furthermore comprising an emulsifying agent.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 01/01176

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K38/14 A61K47/10 A61K47/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SVINHUFVUD, LILLEMOR BORTHEN ET AL: "Effect of topical administration of vancomycin versus chlorhexidine on.alpha.-hemolytic streptococci in oral cavity" ORAL SURG., ORAL MED., ORAL PATHOL. (1988), 66(3), 304-9 , XP001013385 page 306	1,4
Y	--- -/--	1-12

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 August 2001	03/09/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Seegert, K

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 01/01176

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	CORBETT, J. ET AL: "Injectable, absorbable gel -formers for controlled release of antibiotics" PROC. INT. SYMP. CONTROLLED RELEASE BIOACT. MATER. (1998), 25TH, 38-39 , XP001013454 "Experimental Methods" page 38, right-hand column	1,4
Y		1-12
X	US 5 681 873 A (TIPTON ARTHUR J ET AL) 28 October 1997 (1997-10-28) column 17, line 34 - line 39	1,4
Y		1-12
X	WO 99 42083 A (HAU KEE HUNG) 26 August 1999 (1999-08-26) claims	1,4
Y		1-12
P,X	WO 01 12128 A (ATLANTIC BIOMED CORP ;HAU KEE HUNG (US)) 22 February 2001 (2001-02-22) claims	1,4
P,X	WO 01 00226 A (TOA PHARMACEUTICAL CO LTD ;HANAZOME ISAO (JP); KASAMA TOSHIO (JP);) 4 January 2001 (2001-01-04) & DATABASE CHEMICAL ABSTRACTS 'Online! AN 134:61571, abstract	1,3,4
Y	WO 00 33877 A (JOHNSON AND JOHNSON CONSUMER C) 15 June 2000 (2000-06-15) claims	1-12
Y	US 5 314 685 A (TYLE PRAVEEN ET AL) 24 May 1994 (1994-05-24) the whole document	1-12

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte[redacted]onal Application No
PCT/IB 01/01176

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5681873 A	28-10-1997	NONE	
WO 9942083 A	26-08-1999	US 5981499 A	09-11-1999
		AU 7169798 A	06-09-1999
		CN 1226425 A	25-08-1999
		EP 1056442 A	06-12-2000
WO 0112128 A	22-02-2001	US 6248718 B	19-06-2001
		AU 7882600 A	13-03-2001
WO 0100226 A	04-01-2001	JP 2001010971 A	16-01-2001
WO 0033877 A	15-06-2000	US 6238683 B	29-05-2001
		AU 1841200 A	26-06-2000
		BR 9907666 A	19-12-2000
		CN 1292707 T	25-04-2001
		EP 1051193 A	15-11-2000
US 5314685 A	24-05-1994	AU 4282893 A	13-12-1993
		CA 2135598 A	25-11-1993
		EP 0641221 A	08-03-1995
		JP 7508976 T	05-10-1995
		WO 9323083 A	25-11-1993

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

CORRECTED VERSION

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
17 January 2002 (17.01.2002)

PCT

(10) International Publication Number
WO 02/04012 A1

(51) International Patent Classification[7]: A61K 38/14, 47/10, 47/34

(21) International Application Number: PCT/IB01/01176

(22) International Filing Date: 3 July 2001 (03.07.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1360/00 11 July 2000 (11.07.2000) CH

(71) Applicant *(for all designated States except US)*: **MICIO PHARMA CHEMICAL AG** [LI/LI]; c/o Firmata Treuhand Anstalt, Landstrasse 35, Postfach 1138, LI-9490 Vaduz (LI).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **DE TOMMASO, Vincenzo** [IT/IT]; Residenza Alberata, 352, I-20080 Basiglio (IT).

(74) Agents: **KLAUSNER, Erich** et al.; Ufficio Internazionale Brevetti Ing. C. Gregorj S.p.A., Via Dogana, 1, I-20123 Milan (IT).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(48) Date of publication of this corrected version:
4 April 2002

(15) Information about Correction:
see PCT Gazette No. 14/2002 of 4 April 2002, Section II

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/04012 A1

(54) Title: ANHYDROUS PHARMACEUTICAL COMPOSITION OF VANCOMYCIN FOR TOPICAL USE

(57) Abstract: The present invention refers to an anhydrous pharmaceutical composition of vancomycin, in the form of the free base or a pharmaceutically acceptable salt thereof, for topical use.